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(54) Title: COMPOSITION AND METHOD OF TREATING DISEASE WITH EXTRACT OF *MUSACEAS*

(57) Abstract

A pharmaceutical composition containing an extract of *Musaceas*, a method of treating diseases including bacterial infections, psoriasis, lupus, and lung adenocarcinoma, and a method of making a medicament are disclosed.

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COMPOSITION AND METHOD OF TREATING DISEASE WITH EXTRACT OF *MUSACEAS*

Technical Field

The present invention relates to a pharmaceutical composition comprising an extract of Musaceas plant, and a method of treating particular diseases with a formulation of this extract.

Background Art

Tannic acid and tannin complexes are found in the trunk of plants of the Musaceae Family, i.e., *Musa Paradisiaca, Musa Cavendish Enano,* and related Linnaean classifications. Members of this Family are commonly known as plantains.

Tannic acid is known to be useful in a diagnostic test for the detection of cancer. For example, Macartney et al. in *J. Pathol.* (ENGLAND) September 1979, 129 (1) p. 13-20, "Intracellular filaments in human cancer cells: a histological study", discloses that the distribution of intracellular filamentous systems in human breast and colon cancers has been demonstrated by means of the tannic acid-phosphomolybdic acid-milling dye staining technique. Plasma membrane-associated staining is prominent in breast carcinomas and is strongest in anaplastic tumors. Strong staining is also noted in the cells at the margins of the tumors where the malignant cells are invading the surrounding tissues. In colon carcinomas, filaments are mainly restricted to the terminal web region of the cells but dedifferentiation is accompanied by the development of circumferential staining of the cell membrane. The results are discussed in relation to immunohistochemical and electron microscopic studies of contractile proteins in non-muscle cells.

Tannic acid has been shown to inhibit 12-O-tetra-decanoyl-phorbol-13-acetate (TPA) tumor promotion. Perchellet et al., *Basic Life Sci.* (UNITED STATES) 1992, 59 p. 783-801, discloses that naturally occurring plant phenols with antimutagenic and anticarcinogenic activities were tested for their abilities to inhibit the biochemical and biological effects of the potent tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate (TPA) in mouse epidermis in vivo. When applied topically to mouse skin, tannic acid (TA), ellagic acid, and several gallic acid derivatives all inhibited TPA-induced ornithine decarboxylase activity, hydroperoxide production, and DNA synthesis, three biochemical markers of skin tumor promotion. In a two-step initiation-promotion protocol, the same phenolic compounds also inhibited the incidence and yield of skin tumors promoted by TPA.

Ramanathan et al. in "Cytotoxic effect of plant polyphenols and fat-soluble vitamins on malignant human cultured cells", *Cancer Lett.* (NETHERLANDS) Mar. 15, 1992, 62 (3) p. 217-24, discloses in vitro studies which showed that several flavonoids, tannic acid, gallic acid and fat-soluble vitamins inhibited HeLa and Raji lymphoma cell growth. The inhibition trend exhibited by these

compounds was similar for both cell lines, and their growth was inhibited dose dependently. Butein, (10 microM), the most potent anti-proliferative agent, exerted 30% growth inhibition and was more effective on HeLa cells. Retinol (100 microM) inhibited cell proliferation completely. Tannic acid was twice as potent as its monomer gallic acid. From structure-activity consideration, the C 2,3-double bond of the flavonoid molecule was important for activity. Flavonoid aglycones were more effective than their corresponding glycosides in suppressing cell growth in vitro. No in vivo results were presented.

Athar et al., "Effect of dietary tannic acid on epidermal, lung, and forestomach polycyclic aromatic hydrocarbon metabolism and tumorigenicity in Sencar mice," *Cancer Res.* (UNITED STATES) Nov. 1, 1989, 49 (21) p. 5784-8, discloses tannic acid inhibits the mutagenicity of several polycyclic aromatic hydrocarbons (PAHs) and their bay-region diol-epoxides. Studies have shown that when applied topically to Sencar mice, tannic acid caused substantial inhibition of epidermal PAH metabolism, subsequent PAH-DNA adduct formation, and PAH-induced skin carcinogenesis. However, initiation and promotion of tumors are distinguishable stages of carcinogenesis, quite different from attenuation of growth of existing tumors, or remission of cancer. That is, remission of tumors and other cancer is a process unrelated to the initiation and promotion of cancer. Athar et al. addresses the rate of tumor formation in mice. These authors used a concentration of 1% tannic acid in the feed for a total dose of about of 50 mg per day for evaluation of induction of lung and forestomach tumors in mice. Tables 2 and 3 of Athar disclose a reduction of the incidence of tumors per mouse in the group treated with 1% tannic acid. Thus, Athar's work addresses the formation of tumors, *but not the regression* of tumors. Athar et al. discloses a reduction in carcinogenesis in mice. Athar et al. does not disclose or suggest the use of an extract of *Musaceas* formulated as a pharmaceutical composition comprising tannic acid, tannin complexes, and/ or gallic acid. Most importantly, Athar et al. does not disclose or suggest the effect on *existing* tumors or other diseases, of an extract of *Musaceas* containing tannic acid, tannin complexes and/ or gallic acid. None of the above publications disclose that either an extract of *Musaceas*, tannic acid, tannin complexes, or gallic acid are useful for the ***treatment*** of existing cancer or other diseases.

Current standard cancer treatments include surgery, chemotherapy and radiation therapy, which often present patients with unpleasant side effects and, depending on the type of cancer may have limited effectiveness as treatments.

There is thus a need in the art for proven effective treatments, with limited unpleasant side effects, for many types of cancer and other diseases that may have their origins in poorly regulated cell growth. The *Musaceas* extract pharmaceutical composition and method of the present invention overcomes the deficiencies in the prior art compounds.

Disclosure of Invention

It is an object of the present invention to provide a pharmaceutical composition for the treatment of cancer comprising tannic acid or tannin complexes from the sap of a plant of the Musaceae Family and a pharmaceutically acceptable carrier. The plant is preferably selected from the group consisting of *Musa paradisiaca* (plantain); *Musa Cavendish Enano* (banana), varieties and mixtures thereof.

It is an object of the present invention to provide a method of treating cancer and other diseases comprising administering an effective amount of a pharmaceutical composition comprising an extract of *Musaceas*. The extract contains tannic acid, gallic acid, and/or tannin complexes. It is preferred that the pharmaceutical composition is administered at least once daily, and more preferred that the composition is administered four times daily.

The pharmaceutical composition of the invention is advantageously used to treat any cancer condition and several other diseases. It is to be understood that the invention includes a method of making a medicament for treating cancer and other diseases. The invention includes a pharmaceutical composition comprising an extract of *Musaceas* known to contain tannic acid, gallic acid, and/or tannin complexes, and treatment of a patient with a composition in accordance with the invention.

Types of cancer which may be treated with the composition and method of the present invention include, but are not limited to the following: Nasal cavity, paranasal sinus, nasopharynx, oral cavity and oropharynx squamous cell carcinomas and adenocarcinomas; oral lymphomas; adenoid cystic carcinoma; paragangliomas; squamous cell carcinoma, adenocarcinoma, large cell (undifferentiated) carcinoma , and small cell carcinoma of the lung; mediastinal thymomas, lymphomas and neurogenic carcinomas; squamous cell carcinoma and adenocarcinoma of the esophagus; adenocarcinoma of the stomach; ductal adenocarcinoma, mucinous cystadenocarcinoma, acinar cell carcinoma, unclassified large cell carcinoma, small cell carcinoma, and pancreatoblastoma of the pancreas; hepatocellular carcinoma, hepatoblastoma, cholangiocarcinoma, cholangiocellular carcinoma, cystadenocarcinoma, squamous cell carcinoma, angiosarcoma, hemangioendothelioma, leiomyosarcoma, malignant schwannoma, fibrosarcoma, malignant fibrous histiocytoma, lymphoma, osteosarcoma, rhabdomyosarcoma and mesenchymal sarcoma of the liver; adenosarcoma, squamous cell carcinoma, adenosquamous carcinoma, oat cell carcinoma (small cell), carcinosarcoma, malignant lymphoma, malignant melanoma, rhabdomyosarcoma, fibrous histiocytoma, and angiosarcoma of the gallbladder; adenocarcinoma, fibrosarcoma, leiomyosarcoma, liposarcoma, angiosarcoma, lymphangiosarcoma, lymphoma, and neurofibrosarcoma of the small bowel; adenocarcinoma, mucinous adenocarcinoma, signet-ring cell adenocarcinoma, squamous cell carcinoma, adenosquamous carcinoma, undifferentiated carcinoma, unclassified carcinoma, argentaffin carcinoid tumor, nonargentaffin carcinoid tumor, composite carcinoid tumor, and leiomyosarcoma of the large intestine; squamous cell carcinoma, transitional (cloacogenic) carcinoma, adenocarcinoma, papillary villous carcinoma, and mucinous adenocarcinoma of the anus; renal clear cell, granular cell and sarcomatoid carcinoma; nephroblastoma; transitional cell carcinoma of the ureter; carcinoma of the bladder; adenocarcinoma of the prostate; squamous cell carcinoma and adenocarcinoma of the cervix; adenocarcinoma, cystadenocarcinoma, carcinoma, and adenofibroma, cystadenofibroma, sarcoma, and adenoacanthoma of the ovary; papillary, follicular, and medullary carcinoma of the thyroid; adenoma and carcinoma of the parathyroid; adenoma and carcinoma of the adrenal cortex; fibrosarcoma, and fibrous histiocytoma, liposarcoma, squamous cell carcinoma, and sarcoma of soft tissues; leiomyosarcoma, and rhabdomyosarcoma of muscle tissues; osteogenic sarcoma, fibrosarcoma, fibrous

histiocytoma and chondrosarcoma of bone; angiosarcoma, lymphangiosarcoma, and Kaposi's sarcoma; malignant glomus tumor and hemangiopericytoma; synovial sarcoma and giant cell tumor of the tendon sheath; malignant peripheral nerve sheath tumor, neurofibrosarcoma, malignant triton tumor, malignant glandular schwannoma, epithelioid schwannoma, malignant granular cell tumor, nerve clear cell sarcoma, and malignant paraganglioma; chondrosarcoma and osteosarcoma; malignant mesencymoma; Hodgkin's and non-Hodgkin's lymphoma; cutaneous T-cell lymphoma; Burkitt's lymphoma; primary nervous system lymphoma; acute myelocytic, acute lymphoblastic, chronic myelocytic, chronic lymphoblastic, chronic myelogenous, acute myelogenous, acute promyelocytic, acute nonlymphocytic, acute monocytic, and acute myelocytic leukemia; retinoblastoma; malignant melanoma of the choroid; macroglobulinemia; heavy chain disease; and multiple myeloma.

Another embodiment of the invention is for non-cancer diseases and syndromes. In one embodiment, the invention is useful for the treatment of bacterial infection where that infection is associated with *Bacillus*, *Escherichia*, *Klebsiella*, *Pseudomonas*, *Salmonella*, *Shigella*, *Staphylococcus*, *Streptococcus* or infections resulting from multiple pathogens. Moreover, the invention is suitable for the treatment of burns and other skin wounds that may, or may not, be infected with bacteria. In yet another embodiment of the invention, the extract of *Musaceas* is formulated as a pharmacologic composition suitable for the treatment of ulcerative colitis and varicose ulcers. Furthermore, the invention is suitable for treatment of certain neurodegenerative diseases including but not limited to Parkinson's disease. Another embodiment of the invention is used for the treatment of skin disorders including but not limited to psoriasis. Still another embodiment of the invention is that the invention is used to treat autoimmune diseases including but not limited to lupus and AIDS. In the treatment of non-cancer diseases the *Musaceas* extract is administered for a three-month period as a supplement to conventional therapy.

In an alternative embodiment the invention provides a method of stripping N-acetyl neuraminic acid from a cancer cell surface, thereby allowing recognition of the cancer cell by the immune system in vivo comprising contacting said cancer cell with tannic acid, gallic acid, and/or tannin complexes.

The above and other objects of the invention will become readily apparent to those of skill in the relevant art from the following detailed description and figures, wherein only the preferred embodiments of the invention are shown and described, simply by way of illustration of the best mode of carrying out the invention. As is readily recognized, the invention is capable of modifications within the skill of the relevant art without departing from the spirit and scope of the invention.

The present invention relates to pharmaceutical compositions comprising an extract of *Musaceas* having tannic acid, gallic acid, tannin complexes or mixtures thereof, and a method of treating cancer and other diseases with plant extracts containing tannic acid, gallic acid, and/or tannin complexes. The invention will now be described in a manner to enable production and use of the tannic acid, gallic acid, and/or tannin complex-containing compositions for the treatment of cancer and specific other diseases. Tannin complex compositions as used herein means hydrolyzable tannins, such as esters of sugars, usually glucose.

What is known about the cancer cells' adhesion and their invasive and metastatic growth potential in human tumors? Tumor cells produce an outer protective covering which camouflages the cancer cells epitope structure so the immune system cannot recognize the cells. The protective coating contains N-acetylneuraminic acid in a linear homopolymer of 2-8 linked N-acetylneuraminic acid (NeuNAc) which is referred to as polysialic acid (PSA). PSA is expressed on the adhesion molecule NCAM (Neural Cell Adhesion Molecule) and most cell adhesion molecules. In the cancer patient, PSA is found in extremely elevated blood levels as well as bound to erythrocytes and other blood components vital to the immune response.

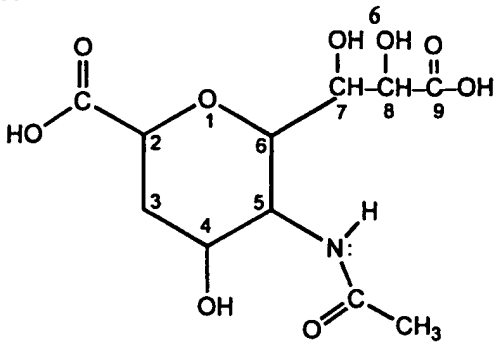
It has been shown experimentally that PSA-NCAM drastically increases cell to cell distances and decreases the adhesion potential on NCAM. One of the vehicles for this physiological change is the hydrated volume of PSA in PSA-NCAM versus NCAM in adjacent cells. The presence of PSA decreases adhesion via physical impedance of overall membrane contacts. These modulatory effects of PSA are relevant to cell migration, establishment of temporal cell-cell contacts, and cellular differentiation during embryonic development.

In the cancer patient, the presence of PSA is linked to a loss of adhesion potential which facilitates the invasive and metastatic growth of the tumors as well as potential structural differentiation and reorganization of healthy cells into tumor cells, i.e. neoplastic cells.

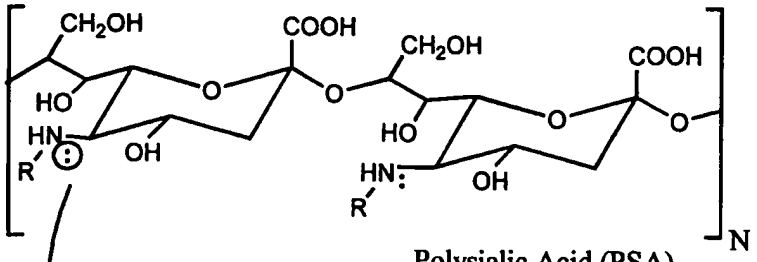
PSA is the principal molecule involved in the masking of the tumor-specific antigens (TA) which normally binds to immune system components, decreasing the effectiveness of NCAM and other cell adhesion molecules, and inducing differentiation of healthy cells into neoplasts. Thus, if one can obtain selective removal of PSA from tissues and the bloodstream where possible, the major limitation that makes cancer difficult to cure, outside of operative conditions, would be eliminated. This would allow the body to attack and destroy a tumor in much the same way it rejects a transplanted organ.

Tannic acid, gallic acid, and tannin complexes in accordance with the present invention bind to and precipitates N-acetylneuraminic acid bound in PSA-NCAM as well as in circulating blood and bound to erythrocytes. Tannic acid recognizes the linear homopolymer of 2-8 linked N-acetylneuraminic acid, with the exposed amino group at the fifth (5) position, as an amino acid chain (protein).

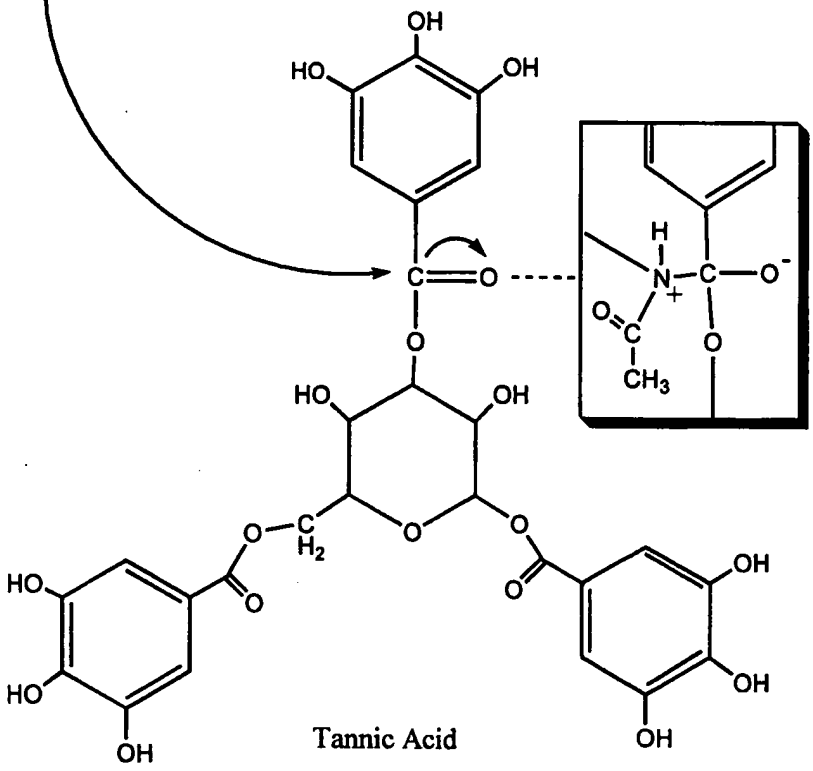
The valent electrons on the nitrogen group of PSA bind covalently to the carbonyl group of tannic acid, linking the chains of the tannic acid moiety. The resulting bond is a very stable one with several resonance structures. See scheme 1 below.



N-Acetylneuraminic Acid



Polysialic Acid (PSA)



Tannic Acid

Three moles of N-acetylneuraminic acid are bound to each mole of tannic acid in solution. The binding of tannic acid and the depolymerization of PSA under mildly acidic conditions provides evidence

that the reaction between tannic acid and PSA (leading to precipitation of three moles of N-acetylneuraminic acid for every mole of tannic acid) is a highly favored and facilitated reaction.

The tannic acid, gallic acid, and tannin complexes act by stripping N-acetylneuraminic acid from the cell surface moiety. The tannic acid, therefore, acts as an astringent. In so doing, tannic acid and tannin complexes affect the cell changes discussed previously, allowing the body's own immune system to reject cancerous growth in much the same way it rejects any foreign invader.

The extract containing tannic acid, gallic acid, and tannin complexes of the present invention exposes cancer cell epitopes that were previously camouflaged by the PSA. At the same time tannic acid, gallic acid, and tannin complexes elevate the immune response by freeing the circulating blood components from bound PSA.

The predominant target of PSA in its propagation of an immune deficient condition in cancer patients is the macrophage, a cell that not only phagocytizes unfriendly cells but also activates the cell-mediated and humoral-immune response. It is believed that the cancer cell, by the secretion of N-acetylneuraminic acid and its polymerization into PSA, induces an immune deficiency that is reversed by the action of tannic acid and tannin complexes.

Method of Production of Tannic Acid Product

Thus the tannic acid, gallic acid, and tannin complexes of the present invention may be formulated into a pharmaceutical composition for the treatment of cancer and other diseases. Tannic acid, gallic acid, and/or tannin complexes in accordance with the present invention may be produced by extraction of *Musaceas*. To obtain tannic acid, gallic acid, and/or tannin complexes from natural sources, the following procedure is followed.

To obtain the active tannic acid, gallic acid, and/or tannin complexes, the trunk of any of the plants of the Musaceae Family, for example, but not limited to *Musa Paradisiaca*, *Musa Cavendish Enano*, and related Linnaean Classifications, are milled to extract the sap of the plant. The pulp is filtered out of the sap to obtain a clear, characteristic tan liquid.

This liquid is preferably incorporated into a standard pharmaceutical preparation containing as its base: sorbitol 70% solution (about 21%), partially hydrogenated castor oil such as that sold under the trademark Cremophor RH40 (about 8.8%), potassium sorbate (about 0.15%), methylparaben (about 0.038%), and propylparaben (about 0.013%) w/w (weight to weight). The batching procedure is a United States Food and Drug Administration (FDA) approved, Current Good Manufacturing Practices (CGMP), standard operating procedure (SOP) for liquid pharmaceuticals. The total percent of tannic acid, gallic acid, or tannin complex in the final product should be about 2.5-20 percent. Preferably the amount of tannic acid or tannin complex in the final product is about 3.0-10 percent concentration, most preferred is about 5% tannic acid, gallic acid, and/or tannin complex based on total concentration of 100% when the active agent is in the presence of a pharmaceutical carrier.

If the natural sources yield a percentage lower than 5%, a food grade tannic acid may be used to yield a 5% concentration. If the natural source yields a higher percentage than 5%, the product may be diluted and retested to assure a 5% concentration.

To prepare tannic acid, gallic acid, and tannin complexes from a synthetic source, the following batching procedure is an FDA approved, CGMP, SOP for liquid pharmaceuticals. Food Grade Tannic Acid is dissolved into water along with the standard pharmaceutical preparation as described under the natural extract. The percent tannic acid in final product is about 5 percent (5%). Tannic acid ($C_{76}H_{52}O_{18}$) may be produced synthetically as described in references cited in the Merck Index 11th Ed., abstract 9023, p. 1431, Merck Publishing Company 1989, (incorporated herein by reference in its entirety).

Further, the pharmaceutical compositions of the present invention are useful for systemic administration to humans and animals in unit dosage forms, such as tablets, capsules, pills, powders, granules, suppositories, sterile parenteral solutions or suspensions, sterile non-parenteral solutions or suspensions oral solutions or suspensions, oil in water or water in oil emulsions and the like, containing suitable quantities of an active ingredient.

Either fluid or solid unit dosage forms can be readily prepared for oral administration. For example, the tannic acid or tannin complex compounds of the invention can be mixed with conventional ingredients such as dicalcium phosphate, magnesium aluminum silicate, magnesium stearate, calcium sulfate, starch, talc, lactose, acacia, methyl cellulose and functionally similar materials as pharmaceutical excipients or carriers. A sustained release formulation can optionally be used. Capsules can be formulated by mixing the compound with a pharmaceutical diluent that is inert and inserting this mixture into a hard gelatin capsule having the appropriate size. If soft capsules are desired, a slurry of the compound with an acceptable vegetable, light petroleum, or other inert oil can be encapsulated by machine into a gelatin capsule.

Suspensions, syrups and elixirs can be used for oral administration of fluid unit dosage forms. A fluid preparation including oil can be used for oil soluble forms. A vegetable oil such as corn oil, peanut oil or sunflower oil, for example, together with flavoring agents, sweeteners and any preservatives produces an acceptable fluid preparation. A surfactant can be added to water to form a syrup for fluid unit dosages. Aqueous alcoholic pharmaceutical preparations may be used having an acceptable sweetener such as sugar, saccharin or a biological sweetener and a flavoring agent in the form of an elixir.

Pharmaceutical compositions for parenteral and suppository administration can also be obtained using techniques standard in the art. The tannic acid and tannin complexes can be present in the reservoir alone or in combination form with pharmaceutical carriers. The pharmaceutical carriers acceptable for the purpose of this invention are the art known carriers that do not adversely affect the drug, the host, or the material comprising the drug delivery device. Suitable pharmaceutical carriers include sterile water; saline, dextrose; dextrose in water or saline; condensation products of castor oil and ethylene oxide combining about 30 to about 35 moles of ethylene oxide per mole of castor oil; liquid acid; lower

alkanols; vegetable oils such as corn oil; peanut oil, sesame oil and the like, with emulsifiers such as mono- or di-glycerides of a fatty acid, or a phosphatide, e.g., lecithin, and the like; glycols; polyalkylene glycols; aqueous media in the presence of a suspending agent, for example, sodium carboxymethyl-cellulose; sodium alginate; poly(vinylpyrolidone); and the like, alone, or with suitable dispensing agents such as lecithin; polyoxyethylene stearate; and the like. The carrier can also contain adjuvants such as preserving, stabilizing, wetting, emulsifying agents and the like.

Additional formulations for administration can be made in accordance with methods and amounts known in the art as set forth in Remington's Pharmaceutical Sciences, 18th Ed., Wiley Publishing (1990) incorporated herein by reference in its entirety.

Table 1 below represents recommended dosages, methods and times of administration of the *Musaceas* extract formulated as a plantain syrup in accordance with the present invention.

TABLE 1

Recommended Dosage of Plantain Syrup for Cancer Treatment

						Before meals and at bed time			
		Weight		Height		4 Times a day (ml)			
Category	**Age**	**Kg**	**lb.**	**cm**	**in.**	**(1)**	**(2)**	**(3)**	**(4)**
Infants	0.5-10	9	20	71	28	4	8	12	16
Children	1-3	13	29	90	35	6	12	17	23
	4-6	20	44	112	44	9	18	26	35
	7-10	28	62	132	52	13	25	37	50
Males	11-14	45	99	157	62	40	60	80	120
	15-18	66	145	176	69	58	87	116	174
	19-24	72	160	177	79	64	96	128	192
	25-50	79	174	176	70	70	104	139	209
	51+	77	170	173	68	68	102	136	204
Females	11-14	46	101	157	62	40	61	81	121
	15-18	55	120	163	64	48	72	96	144
	19-24	58	128	164	65	51	77	102	153
	25-50	63	138	163	64	55	83	110	165
	51+	65	143	160	63	57	86	114	171

Dosage

1. Cancer Stage 1 and other disorders during the 3 months -- used as prophylactic in cancer and other diseases.

2. Cancer Stage 2 and 3 during 3 months and continue with dosage (1) during another 3 months.

3. If the cancer patient has been treated with chemotherapy or radiotherapy this dosage is for three months and three months more with dosage (2). Then three additional months with dosage (1), i.e. 9 months in total.

4. Cancers in Stage 4 are terminal care, with treatment administered for a year.

5. All these dosages may be modified by the physician using methods known in the art, after each monthly checkup. Dosages range from about 4 to about 200 ml. Maximum dosages for height and weight appear in column 4 above.

Diseases other than cancer are treated according to the same schedule as above using stage 1 dosages. In these treatments, the treatment is continued for 3 months and repeated as necessary.

Examples

The following examples are intended to show the use of the composition and method of the invention for treating a variety of diseases. These examples show how the composition and method may be used, but are not intended to limit the uses thereof. Except as noted, 10% concentration of tannic acid was used in all of the clinical studies set forth below.

Patient #1: 79 year old male, Prostate Carcinoma, permanent catheter was surgically inserted. Cancer was inoperative because of cardiovascular condition. Therapy in accordance with the present invention was administered at the maximum dosage for the initial three month period according to "dosage administration." Two weeks after initiation of therapy in accordance with the invention catheter was removed. Cancer was cured and the patient returned to normal activities with the first treatment period, three months. After that, he used the product for 7 additional months.

Patient #2: 43 year old female, Breast carcinoma. Surgery was performed Jan. 11, 1982 on left breast. The problem of metastatic growth was a concern. Therapy in accordance with the invention was initiated for a minimal 3 month period based on patient weight, height criteria. No additional cancerous growths were detected anywhere in her body.

Patient #3: 51 year old female, Breast Carcinoma. Cancer diagnosed at the Cancer Institute of Havana in the left breast. Tumor measured 5 cms by 5 cms. Patient refused removal of breast and therapy in accordance the invention was administered. Therapy in accordance with the invention was initiated based on weight/height criteria at maximum levels (see Table 1, column 4). Tumor diminished in size after first three month interval to the point where it was very difficult to detect by manual examination. Therapy in

accordance with the invention continued according to "dosage administration" for a period of one year. Cancer never returned to this day.

Patient #4: 54 year old female, Colon Carcinoma. She was administered 72 chemotherapy dosages simultaneously with the therapy in accordance with the invention. Her blood work throughout the chemotherapy/therapy was normal. She continued regular checkups and all have been negative. Maximum therapy in accordance with the invention was administered along with the chemotherapy.

Patient #5: 52 year old female, Carcinoma of the uterus. Surgery to remove the uterus was recommended and an operation planned. Upon opening patient, metastatic growth throughout internal organs was detected. Uterus was not removed and patient was classified terminal. Maximum therapy in accordance with the invention levels were administered for a period of one year. She was cured of the cancer throughout her body. Yearly checkups have confirmed no relapse.

Patient #6: 50 year old female. Breast Carcinoma. Operated for removal of left mammary gland in 1981. In 1982 they found the right mammary gland was also infected with cancer. Operation to remove was not an option because metastasis was detected in the skeletal system, lungs and the liver. She was classified terminal. Maximum therapy in accordance with the invention was applied for a period of one year, in which time, she was cured of cancer in all organs. Semi-annual check-ups reveal no relapse.

Patient #7: 67 year old female. Carcinoma of the uterus. Cancer was pervasive throughout organ. Radiation therapy was prescribed. She had such a violent reaction to the radiation that she refused further treatment. She underwent therapy in accordance with the invention at maximum dosage for a period of one year. No other treatments were applied. Semi-annual checkups reveal no relapse.

Patient #8: 2 year old boy. Acute Lymphocytic Leukemia. Patient classified as terminal. Therapy in accordance with the invention was initiated by drop-wise administration because patient was having difficulty swallowing. Administration was continued until patient was able to swallow dosage after 1 week. Therapy period was one year at maximum dosage as per weight/height criteria. Patient initially showed signs of being cured. Relapse occurred two years after completion of therapy through a process where the leukemia cells encysted in the testes. Cyst ruptured at the time of relapse. Therapy in accordance with the invention was re-administered and patient was cured through a year long treatment period. To this date, all check-ups have been negative. Patient is now 17 years old.

Patient #9: 56 year old female. Colon Carcinoma. Experienced bowel blockage. Diverted passage of refuse but did not remove tumor. Tumor was so large that removal was not feasible. Surgery was performed to extend her life without hope of cure. Doctors opted to bypass chemotherapy and radiation

therapy fearing results of extended therapy would be devastating. Therapy in accordance with the invention was administered at maximum level for a period of one year. Tumor disappeared and has not returned.

Patient #10: 38 year old female. Cancerous Lesion of the Tongue. The lesion was about the size of a penny. Over the course of six months, conventional treatment was ineffective. The lesion grew deeper into the tongue. Therapy in accordance with the invention was administered over 3 months at stage 1 with weight/height criteria. The lesion healed and the tissue of the tongue was restored to normal. No relapse.

Patient 11: 64 year old male. Carcinoma of penis. Surgery was performed to remove sexual organs (testes and penis). They found that the cancer metastasized and the patient was classified terminal. Therapy in accordance with the invention was administered at maximum levels immediately after surgery for one year. He has had no relapse and is cured of the cancer that was diagnosed after his surgery.

Patient #12: 5 year old boy. Acute Lymphocytic Leukemia. Therapy in accordance with the invention was administered at maximum level according to weight/height criteria for one year. Patient initially showed signs of being cured. Relapse occurred about 2 years after completion of therapy in accordance with the invention through a process where the leukemia cells encysted in the testes. Cysts ruptured at the time of relapse. As in Patient #8, therapy in accordance with the invention was re-administered through a period of one year. Patient was cured and subsequent check-ups have been negative. Patient is now 20 years old.

Patient #13: 4 year old female. Acute Lymphocytic Leukemia. Chemotherapy had been administered. The patient's overall reaction to the chemotherapy was very violent. There was no improvement with the chemotherapy. Therapy in accordance with the invention was administered and immediately overall blood work returned to normal parameters. Therapy in accordance with the invention was administered for one year at maximum levels according to weight/height criteria. Patient (now 19 and married) was cured of cancer and no relapse has occurred.

Patient #14: 21 year old male. Hodgkin's Lymphoma. Chemotherapy was initially applied with no improvement to condition of the disease and a devastating reaction to the chemotherapy. On patient's authority, chemotherapy was discontinued and therapy in accordance with the invention was administered according to weight/height criteria for one year. Even though patient was considered terminal prior to therapy in accordance with the invention, he was cured of disease. Subsequent check-ups have been negative and no relapse has been recorded.

Patient #15: 58 year old female. Breast carcinoma. Left mammary gland was removed and because of fear of metastasis, therapy in accordance with the invention was administered for a period of one year according to weight/height criteria. At the end of the therapy in accordance with the invention, no cancer was detected. Two years after therapy in accordance with the invention on yearly check-ups, it was discovered that she had carcinoma of the uterus. Therapy in accordance with the invention was re-administered for a period of one year. She was cured of uterine cancer and ongoing check-ups have been negative. Great concern was expressed about the possibility of metastasis but none occurred.

Patient #16: 59 year old female. Carcinoma of the Breast with metastasis in both lungs and lymph nodes. Attending physician detected cancer initially in the lungs, but primary site was in the breast. Patient was classified terminal. Therapy in accordance with the invention was administered at maximum levels according to weight/height criteria for a period of one and one half year. At the end of therapy in accordance with the invention, the Doctor declared patient cured, and was impressed by the therapy. All check-ups have since been negative for cancer.

Patient #17: 4 year old female. Monoblastic Leukemia. Chemotherapy was administered with no improvement to her condition, but devastating to her well being. Oral chemotherapy maintenance was discontinued by parents with only the three month periodic treatment at ongoing check-ups. No improvement to her condition was reported. Therapy in accordance with the invention was initiated at maximum levels according to weight/height criteria for a period of one year. She was cured of monoblastic Leukemia and has had no relapse.

Patient #18: 41 year old female. Liposarcoma of the right thigh. She underwent two unsuccessful operations to remove cancer with condition returning each time. Amputation was recommended for patient's survival, but patient refused. Therapy in accordance with the invention was administered at maximum levels according to weight/height criteria for a period of one year. She was cured of cancer, and has had no relapse. Patient is 54 years old and doing well.

Patient #19: 51 year old female. Multiple Myelomas. Patient was unable to walk due to metastasis in hips and ribs. No other therapy was administered but the therapy which was given at maximum levels for a three month period. Doctors examined X-rays taken at the end of the therapy, and all concurred on actual regeneration of skeletal tissue and structure. Patient's family never revealed to her that she had cancer. The therapy was designed for a one year period, but patient refused treatment after three months because she had gained weight. Patient died four years later of Myeloma.

Patient #20: 30 year old male. Hypernephroma (Cancer of Kidney). The Chief of Oncology and patient's relative were the attending physicians. Metastasis occurred in both the lungs and ribs (liver and brain

were also suspected). Patient was given less than one month to live and was classified terminal. Therapy in accordance with the invention was administered at maximum levels according to weight/height criteria for a period of one year. After 20 days of therapy in accordance with the invention, regeneration of ribs had occurred, and after one month the patient had returned to normal daily activities. At three months, the therapy was discontinued due to matters beyond patient's control. The patient lived for two years after therapy, and never experienced any pain from the relapse.

Patient #21: 27 year old male. Carcinoma of the Bladder. Patient was the first to receive therapy (in 1951). Attending Urologist, diagnosed carcinoma which was confirmed by two other physicians. All three physicians performed a cystoscopic examination. The carcinoma was located on the right wall of the neck of the bladder. Patient's symptoms were painful urination with high levels of blood in urine. Surgery was recommended by all three physicians. Patient refused surgery and therapy in accordance with the invention was administered at maximum dosage according to weight/height criteria. Regular three month check-ups were performed which included a cystoscopic exam each time, and at the first check-up the carcinoma had diminished in size. At 10 months, patient was released from physicians care and declared cured of cancer spontaneously (physicians were unaware of therapy). The patient married a short time later, had four healthy children, and is currently 71 years old and has suffered no relapses.

Treatments of patients may also be made with a composition according to the invention wherein the composition comprises about 5% tannic acid, gallic acid, or tannin complex.

Patient #22: 50 year old male. Adenocarcinoma of the large bowel. Therapy is administered in accordance with the invention, with a 5% tannin complex being provided to the patient. Tumor shrinkage is observed as a result of six months of treatment.

Patient #23: 52 year old male. Squamous cell carcinoma of the gallbladder. Therapy is administered in accordance with the invention, with a 5% tannin complex being provided to the patient. Tumor shrinkage is observed as a result of five months of treatment.

Patient #24: 54 year old male. Ductal adenocarcinoma of the pancreas. Therapy is administered in accordance with the invention, with a 5% tannin complex being provided to the patient. Tumor growth is greatly retarded as a result of eight months of treatment.

Patient #25: 60 year old female. Squamous cell carcinoma of the cervix. Therapy is administered in accordance with the invention, with a 5% tannin complex being provided to the patient. Tumor shrinkage is observed as a result of six months of treatment.

Patient #26: 32 year old male. Osteogenic sarcoma. Subsequent to amputation of the patient's leg, the sarcoma appears to have metastasized. Therapy is administered in accordance with the invention, with a

5% tannin complex being provided to the patient. Remission from metastatic neoplasm is observed as a result of six months of treatment.

Patient #27: 45 year old female. Leiomyosarcoma of the small bowel. Therapy is administered in accordance with the invention, with a 5% tannin complex being provided to the patient. Remission is observed as a result of five months of treatment.

Patient#28: 42 year old female. Lung adenocarcinoma of the left lung. Diagnosis is confirmed by pathology of a biopsied lung specimen. Therapy is administered in accordance with the invention. The effect of the therapy on the cancer is observed at half yearly intervals for more than three years.

Patient#29: 51 year old female. Lupus erythematosus. Therapy is administered in accordance with the invention for a period of three months as a supplement to conventional therapy. The inflammation of the atrophic scarred legions is monitored over a period of 15 months.

Patient#30: 4 year old boy. Enteritis. *Salmonella brancaster* identified on seroculture. Therapy is administered in accordance with the invention for three months. Specimens are monitored for *Salmonella.*

Patient#31: 13 year old female. Focal skin burn lesions infected with *Klebsiella* sp. Therapy is administered in accordance with the invention. The area of lesions is measured by planimetry.

Patient #32: 62 year old male. Parkinson's Disease. Therapy is administered in accordance with the invention, concomitant with conventional therapy. Symptoms are observed over the course of 16 months.

Patient #33: 59 year old female. Psoriasis. Therapy is administered in accordance with the invention concomitant with supportive therapy. The disease is monitored over the course of five years.

Patient #34: 51 year old male. Ulcerative colitis. Therapy is administered in accordance with the invention concomitant with conventional therapy. The disease is monitored over the course of three years.

Patient #35: 48 year old female. Anemia. Therapy is administered in accordance with the invention concomitant with conventional therapy. The disease is monitored over the course of six years.

Patient #36: 66 year old male. Varicose ulcers. Patient reports a life-long history of smoking. Therapy is administered in accordance with the invention, concomitant with conventional therapy. Patient also enrolls in a smoking cessation program. The ulcer size is measured over the course of eighteen months.

Patient #37: 31 year old male. AIDS. Therapy is administered in accordance with the invention, concomitant with conventional therapy. The disease is monitored over the course of five years.

Experimental Example 1. Effect of pharmaceutical composition on cell growth. Extract of *Musaceas* is formulated with sorbitol as a composition containing 5% tannic acid. The solution is filtered through sterile 0.22 micron cellulose acetate membrane (Beckton-Dickenson Falcon 7111) and secondarily filtered through a 0.2 micron low protein binding non-pyrogenic filter (Gelman Sciences). The effect of various concentrations of the pharmaceutical composition on NLF Neuroblastoma cell proliferation is shown in Table 2.

TABLE 2

Inhibition, by *Musaceas* Extract, of [^{3}H] Incorporation into NLF Tumor Cells, and Colony Formation

Concentration	cpm	n	No. colonies
5%	30	3	0
3.3	33	3	40
1.7	35	3	37
0.8	58	2	60
0	60,772	3	80

"Concentration" in Table 2 refers to the concentration of tannic acid in the diluted composition.

The results appear to show a substantial inhibition of tumor cell growth with increasing concentrations of the pharmaceutical composition. A subsequent measurement of quenching showed no statistically significant effect of quenching on the actual counts.

Experimental Example 2. Inhibition of neuroblastoma cell growth by *Musaceas* extract. The effect of extract on NFL neuroblastoma cell growth is measured at greater dilutions of extract, as shown in Table 3. The extract is powerfully biostatic to these cancer-derived cells even when diluted over 14 fold.

TABLE 3

[^{3}H] Incorporation into NFL Neuroblastoma Cells

Conc. (%)	Mean (cpm)	std. dev.
1.4	64	15
0.7	85	24
0.35	105	18
0.175	2679	1977
0.088	10254	4764
0.044	8081	648
0.022	17306	6536
0.011	12639	12414

Experimental Example 3. The anti-tumor efficacy of extract of *Musaceas*. The anti- tumor efficacy of *Musaceous* extract is evaluated using the A549 human lung adenocarcinoma xenotransplantation system. A549 cells (about 7 x 10^6 cells) are administered to the subcutaneous flanks of 21 6-8 week old Balb/c *nu/nu* mice, maintained in accordance with PHS policy and AAALAC principles. The resultant tumors of the A549 cells are measured weekly and tumor volumes calculated. When tumors achieve a size of 75-100mm^3, mice are randomized into one of three groups of 7 mice each.

The pharmaceutical composition of *Musaceas* extract containing sorbitol is filtered sequentially through a coarse filter, a 0.45 micron filter, and a sterile 0.22 micron filter. Solution is diluted with vehicle to achieve working solutions with a concentration of 10mg/ml tannic acid and 2mg/ml tannic acid. The volumes of the preparation administered to mice in the experimental cohort are similar to volumes of vehicle administered to control mice. Group 1 receives 1000mg/kg body weight /day. Group 2 receives 200 mg/kg/day, and control receives vehicle. Mice are weighed weekly and tumor volumes determined weekly for 10 weeks. Mice of each group grow and gain weight. Significant differences in average mouse body weight are not observed between cohorts at any interval. The tumors of control mice grow to a volume of approximately 1100 cubic millimeters within 10 weeks.

As shown in Table 4, significant ($p<0.1$) differences in tumor volume are observed between tumors of mice administered vehicle and mice receiving 1000mg/kg/day by week seven and continuing through week 10. Treatment with the extract at this concentration results in a 68% inhibition in A549 tumor development during the 10 weeks of assessment. Significant differences are not observed between tumors of control mice and mice of the 1000 mg/kg/day group at any weekly interval from week 1 through week 6. Similarly, no significant differences in tumor volume are noted between those of control mice and mice of the 200mg/kg/day group at any interval during the 10 weeks of assessment.

TABLE 4

Group	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Week 9	Week 10
1000 mg/kg day Extract	111±22	141±43	166±77	182±69	239±64	241±94*	271±89*	311±91*	352±199*
200 mg/kg day Extract	118±42	151±85	228±78	326±121	397±99	547±193	605±169	794±299	966±399
Vehicle	114±37	148±51	229±81	349±130	399±98	596±188	677±193	856±349	1101±399

* indicates a significant ($p<0.1$) difference when compared to control.

In sum, the invention provides a pharmaceutical composition including tannic acid, gallic acid, and/or tannin complexes, and a method of treating cancer and other diseases with a plant extract containing tannic acid, gallic acid, and/or tannin complexes, which shows effective results in the treatment of several diseases.

The purpose of the above description and examples is to illustrate some embodiments of the present invention without implying any limitation. It will be apparent to those of skill in the art that various modifications and variations may be made to the composition and method of the present invention without departing from the spirit or scope of the invention. All patents and publications cited herein are incorporated by reference in their entireties.

WHAT IS CLAIMED IS:

1. A method for the treatment of disease, comprising administering to a patient in need thereof an effective amount of a pharmaceutical composition comprising an extract of a plant of the *Musaceas Family* and a pharmaceutically acceptable carrier, and wherein the disease is AIDS, a bacterial infection, a burn wound, anemia, ulcerative colitis, a varicose ulcer, a skin disorder, a neurodegenerative disease, an autoimmune disease, or asthma.

2. The method of claim 1 in which the bacterial infection is associated with *Bacillus, Escherichia, Klebsiella, Pseudomonas, Salmonella, Shigella, Staphylococcus,* or *Streptococcus.*

3. The method of claim 1 in which the neurodegenerative disease is Parkinson's disease.

4. The method of claim 1 in which the skin disorder is psoriasis.

5. The method of claim 1 in which the autoimmune disease is lupus.

6. The method of claim 1 where the pharmaceutical composition is administered orally.

7. The method of claim 1 where the pharmaceutical composition is administered parenterally.

8. The method of claim 1 in which the patient is a human.

9. The method of claim 1 in which the composition is administered at least once daily.

10. A method for the treatment of lung adenocarcinoma, comprising administering to a patient suffering from lung adenocarcinoma an effective amount of a composition comprising an extract of a plant of the *Musaceas* Family.

11. The method of claim 10 in which said composition further comprises a pharmaceutically acceptable carrier.

12. A pharmaceutical composition for the treatment of disease, comprising an extract of a plant of the *Musaceas Family* and a pharmaceutically acceptable carrier.

13. The pharmaceutical composition of claim 12, in which the sap is sterile.

14. The pharmaceutical composition of claim 12, where the plant is selected from the group consisting of:

Musa paradisiaca (plantain),

Musa cavendish enano (banana), and

mixtures thereof.

15. The pharmaceutical composition of claim 12, in which the extract is filtered.

16. The pharmaceutical composition of claim 12, further comprising a preservative.

17. The pharmaceutical composition of claim 12, further comprising a sweetener.

18. The pharmaceutical composition of claim 12, wherein the composition comprises tannic acid, gallic acid, tannin complexes, their salts, or combinations thereof.

19. The pharmaceutical composition according to claim 17, where the sweetener is sorbitol.

20. In a method of preparing a medicament for the treatment of disease including AIDS, lupus, a bacterial infection, a burn wound, a skin disorder, anemia, ulcerative colitis, a varicose ulcer, a neurodegenerative disease, an autoimmune disease, or asthma, which method comprises obtaining an extract of a plant of *Musaceas* and combining it with a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/17677

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 35/78, 39/385
US CL :424/195.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/195.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,&	US 5,773,419 A (FALCON) 30 June 1998 (30.06.98) see entire document.	1-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

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